Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 3-8, 13-19, 36, 37, 59, 63, 64, 69-75 and 79 are pending in the application, with claims 1, 59 and 79 being the independent claims. Claims 2 and 60 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claim 79 is sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112

In the Office Action dated December 17, 2003, the Examiner rejected claims 1-8, 13-19, 36, 37, 59-64 and 69-75 under 35 U.S.C. §112, first paragraph alleging that the specification did not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

More specifically, at page 2, the examiner stated that:

> . . . the specification, while being enabling for methods of determining the effect of a substance on characteristics of Alzheimer's disease in brain cells, does not reasonably provide enablement for any neurodegenerative disease. The only disease correlation that the specification shows between APP and integrin is Alzheimer's disease. Further at the time of filing, the art only recognized Alzheimer's disease has having this correlation. In addition, the only guidance provided in the specification is

> to Alzheimer's disease. The specification provides no guidance as to other characteristics related to other neurological diseases that are modulated by integrins. Only APP, aβ and integrin are taught sufficiently by the specification to provide the guidance needed.
>
> Thus, it would have required an undue amount of experimentation at the time of filing for the skilled artisan to make and use the present invention without having to engage in an undue amount of experimentation lacking a predictable degree of success.

Applicants disagree.

While the methods of the invention should be able to determine the effect of a substance on characteristics of Alzheimer's disease, the invention is not limited solely to such an embodiment. Applicants' specification has provided sufficient information such that one of skill in the art could make and use the claimed invention without undue experimentation to determine the effect of a substance on different neurodegenerative diseases in general, not merely Alzheimer's disease. Additionally, contrary to the Examiner's argument, enablement of the claims does not depend solely on a relationship between APP, integrin and Alzheimer's disease. In any event, without acquiescing in the propriety of the rejection and solely in an effort to expedite prosecution, Applicants have amended claim 1 to delete the recitation "characteristics of neurodegenerative disease" and replaced it with "sequestration, uptake or accumulation of amyloid."

Both the original and amended claim language is supported in the specification, at least as follows:

> 1) Sources of brain cells to be used in the method - pages 31-35.
> 2) Culturing of brain cells for the assays - 35-36.
> 3) Treatment of brain cells with an agent capable of modulating integrins or integrin receptors - pages 36-37.
> 5) determining sequestration, uptake or accumulation of amyloid in brain cells (characteristics of neurodegeneration) pages 38-42.
> 6) Examples and results of the claimed methods- pages 49-54.

The above information provides guidance for each step of the claimed method such that one of skill in the art could practice the invention without undue experimentation. Based on all of the above, the rejection under 112, first paragraph is overcome and should be withdrawn.

Rejections under 35 U.S.C. § 102

In the Office Action at page 3, the Examiner rejected claims 1-4, 7, 8, 13, 16-18, 37, 59-61, 63, 64, 69 and 72-74 under 35 U.S.C. 102(b) as allegedly being anticipated by Harris-White *et al, The Journal of Neurosci. 18*:10366-10374, 1998. Applicants respectfully traverse this rejection.

More specifically, the Examiner stated that: "It is noted to applicant that "condition that modulates integrins or integrin receptors" is disclosed in the specification to include A/β peptide (specification, page 19, parag. 0065, lines 1-4)." This statement appears to be the primary basis for the §102 rejection.

The sentence cited by the Examiner is then followed by: "In addition to the compounds referred to in the earlier paragraph, additional examples of modulatory compounds include amyloid beta peptide, oxidative free radicals . . . β-amyloid . . ." One of skill in the art would readily recognize that the list does not represent compounds that modulate integrin or integrin receptors. Rather, as stated at the end of paragraph 0065, these compounds can be used in combination with the modulatory compounds. Applicants have amended the specification to more clearly state that which is already set forth in paragraph "0065." Support for the changes are found in previous paragraph "0064" that refers to the modulatory compounds and states that "These compounds can

be used individually or in a cocktail containing a combination of more than one compound." Paragraph "0065" now more clearly reflects such combinations.

Because "amyloid beta peptide" is not a "condition that modulates integrins or integrin receptors," the addition by Harris-White of either amyloid beta or TGFβ fails to meet at least one of the limitations of the claimed invention. Additionally, the Examiner has failed to point out the manner in which the cited art teaches the additional limitations of the claimed methods. Therefore, Harris-White does not anticipate the claimed invention, the rejection under §102 cannot stand and the rejection should be withdrawn.

Rejections under 35 U.S.C. § 103

In the Office Action at page 4, the Examiner rejected claims 1, 2, 5, 6, 36 and 59-62 under 35 U.S.C. 103(a) as allegedly being unpatentable over Matter *et al., J. Cell Biology 141*:1019-1030 (hereinafter "Matter"), 1998 in view of Harris-White. Applicants respectfully traverse this rejection.

More specifically, the examiner states that:

> Therefore, it would have been obvious to the ordinary artisan at the time of the instant invention, to perform the analysis of Matter et al using the hippocampal brain slice assay of Harris-White given the motivation of Harris-White that the brain slice assay is more reflective of the in vivo situation than cultured cells.

Applicants disagree.

As noted above in rebutting the § 102 rejection, Aβ is not a modulator of integrin. The use of Matter in the rejection relies on the assumption that Aβ is a modulator of integrin or the integrin receptor and is therefore incorrect. Matter therefore fails to teach or suggest the modulation of integrin as required by claim 1.

Harris-White does not remedy this deficit in Matter. Regardless, even assuming *arguendo*, that Harris-White did remedy all of the deficits in Matter, there would still be no motivation to combine the cited art in order to obtain "a method for determining the effect of a substance" on characteristics of neurodegenerative diseases. Both Harris-White and Matter do no more than report observations on cells or tissues. They do not disclose or suggest, either individually or in combination with each other, providing an assay for determining the effects of substances on amyloid accumulation, sequestration or uptake following modulation of integrins or integrin receptors.

Based on all of the above, this rejection is overcome and should be withdrawn.

In the Office Action at page 5, the Examiner rejected claims 1, 13-15, 59 and 69-71 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Matter in view of Harris-White. Applicants respectfully traverse this rejection.

More specifically, the Examiner states that:

> Therefore, it would have been obvious to the ordinary artisan at the time of the instant invention, to perform the antibody and peptide studies described in Matter using the hippocampal brain slice model of Harris-White given the motivation of Harris-White that the brain slice model is reflective of the in vivo situation than cultured cells.

Applicants disagree.

Regardless of what Matter or Harris-White allegedly disclose, the Examiner has failed to show how the combination of the two publications would teach each and every limitation of the claimed method and that there would be a motivation to make such a combination.

The invention of claim 1 is "a method for determining the effect of a substance on sequestration, uptake or accumulation of amyloid." The combination of cited art fails to

teach such a method. More specifically, the combination of cited art further fails to disclose "exposing brain cells to a condition that modulates integrins or integrin receptors in said cells."

At best, Matter teaches no more than the observation that Aβ when added to cultures affects the amyloid matrix in cells. (pages 1023-1024). According to Matter, the addition of an amyloid antibody decreases formation of such a matrix. This is not the same as "exposing brain cells to a condition that modulates integrins." Regardless of whether Matter allegedly teaches adding an amyloid antibody to a culture or that GRGDSP inhibited Aβ binding to the cell (page 1023, col. 1, parag. 1, lines 23-33), this still fails to disclose Applicants' method. The Examiner may not take disparate independent observations from different pieces of cited art, in an attempt to mix and match and thereby ultimately arrive at Applicants' claimed invention.

Harris-White fails to remedy the deficits of Matter. Therefore, even if Matter was combined with Harris-White, the combination would still fail to disclose all limitations of the rejected claims. Therefore, this rejection is overcome and should be withdrawn.

In the office Action at page 5, the Examiner rejected claims 1, 19, 59 and 75 under 35 U.S.C. §103(a) as allegedly unpatentable over Hass *et al., J. Biol. Chem. 273*: 13892-13897, 1988 in view of Harris-White. Applicants respectfully traverse this rejection.

Specifically, the Examiner argues that:

> Therefore, it would have been obvious to the ordinary artisan at the time of the instant invention, to perform the apoE studies described in Hab [sic] using the hippocampal brain slice model of Harris-White given the motivation of Harris-White that the brain slice model is reflective of the in vivo situation than cultured cells.

Applicants disagree.

At best, Hass does no more than look at the *APOE* gene locus in COS-1 cells. It is quite an extrapolation from an African Green Monkey kidney cell line to the "brain cells" required by the claimed methods. Nowhere in the cited art is there a suggestion to use the observations of Hass in a method using brain cells. Therefore, regardless of what Hass or Harris-White allegedly disclose, the Examiner has failed to show that the combination of the two publications would teach each and every limitation of the claimed methods and that there would be a motivation to make such a combination of art.

The Examiner's alleged motivation for making the combination of the cited art is that "the hippocampal slice model permits conditions most similar to the in vivo situation that also allow for a longer time course for the development of neurotoxicity (page 10369, col. 2, parag. 1, lines 11-14)." Regardless, this still fails to provide motivation to combine Hass with Harris-White to arrive at the claimed invention. It is also not clear from this argument, how or why one extrapolates from Hass. Despite, the above characterization of the "hipocampal slice model," this would still fail to provide motivation to use the results of Hass in an method for determining the effect of a substance on brain cells. Even assuming *arguendo*, that such a combination was made, for at least the reasons argued in the earlier §102 rejection, the combination would still fail to render obvious the claimed invention due to deficiencies in Harris-White. Therefore, this rejection is overcome and should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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